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MOLECULAR DOCKING AND MOLECULAR DYNAMICS STUDIES OF THE NOVEL HU PROTEIN DNA BINDING ABILITY INHIBITORS. INSIGHTS INTO THE INHIBITION MECHANISM AND SELECTIVITY

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The histone-like (HU) protein is one of the major nucleoid-associated proteins involved in DNA supercoiling and compaction into bacterial nucleoid as well as in all DNA-dependent transactions. This small positively charged dimeric protein binds DNA in a non-sequence specific manner promoting DNA super-structure [1]. HU proteins are absent in a eukaryotic cell and therefore provide potential pharmacological targets for the development of antibacterial drugs. In 2014, it was shown that HU protein from M. tuberculosis inhibitors obtained by molecular docking are able to disrupt the structure of the nucleoid and inhibit the growth of the bacterium [2]. This work is devoted to a virtual screening for low-molecular compounds capable of selective interaction with the DNA-recognition loop of the HU protein from mycoplasma S. melliferum (HUSpm) and study of stability of the resulting complexes by molecular dynamics. The structure of HUSpm was modelled by homology with IHF protein (PDB ID 1IHF [3]). The virtual screening for inhibitors with a target-specific profile (binding to DNA-recognition loop of HUSpm) was performed in the data base of commercially available compounds Mcule [4], using Lipinski's rule of five. Selected molecules were docked into the DNA-recognition loop site of HUSpm via AutoDock Vina program. Eventually, four compounds (named here L1, L2, L3, L4) with the highest docking score (ranging from -6.4 to -6.8 kcal/mol) were selected. Stability of HUSpm complexes with four selected ligands was studied using molecular dynamics (MD) simulations. HUSpm model with docked inhibitors was used for MD simulation in water solution, which was carried out with the GROMACS simulation package [5]. AMBER99SB forcefield was used, with a cubic model box and the spc216 water model. 100-ps potential energy minimization was performed to relax the structure and avoid steric clashes in further simulations. Pressure and temperature of the system were set to 1 atm and 300 K by running NPT and NVT simulations (100-ps each) correspondingly. A 10-ns productive MD trajectory was obtained. All calculations were performed using the supercomputer of NRC 'Kurchatov Institute'. Molecular dynamic simulation confirmed the stability of contacts formed between L1-L3 inhibitors and amino acid residues of DNA-recognition loops. The complex HUSpm - Ligand L4 was unstable: during the molecular dynamic simulation, L4 was removed from the initial binding region by a distance of more than 3.6 Å and appeared on the outside of the DNA-binding loop. Thus, molecular dynamics methods have shown that three ligands L1, L2 and L3 are able to bind specifically and stably the DNA-recognition loop of HUSpm by means of hydrophobic and polar interactions and can be proposed as a structural basis for creation of antimycoplasmic agents, whose action is based on inhibition of the DNA-binding ability of HU proteins.

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This work was supported by the Russian Science Foundation [grant 15-14-00063]